REMARKS

By this submission, Applicants request continued examination, withdrawal of the pending Appeal, and reopening of prosecution of the application before the examiner. This submission is responsive within the meaning of 37 CFR 1.111 to the last outstanding Official Action. Applicants request entry of the foregoing amendments, reconsideration and withdrawal of all outstanding rejections, and formal notification of allowance.

Applicants cancel the pending claims in favor of those presented herein. The instant claims more particularly point out and distinctly claim that which Applicants perceive to be their invention.

The instant claims are directed to a tablet and a tableting premix. The claimed tablets and tableting premix are those wherein a neutral microgranule is coated with only a single layer of an active principle mixture. The mixture is a combination of active principle and an optional binder. The tablets and premix further include an excipient in the form of a lubricant, but which is present in the embodiments in very small amounts, i.e., 1% or less (by weight).

As now presented, the coated neutral microgranules are free of additional components such as layers or coatings controlling release of the active principle, or masking its taste. By expressly excluding such components, the instant claims are free of the cited art, particularly *Bhutani* and *Harrison*, and likewise are neither taught nor suggested by the cited combination of *Frost* and *Makino*.

Independent claim 19, its dependent claims 20-27, and independent claim 33 are directed to tablets. Independent claim 28, its dependent claim 29, and independent claim 32 are directed to a tableting premix that can be used to fabricate,

for example, tablets of claims 19-27 and 33. Claims 30-31 are directed to processes for making tablets of claim 19.

The tablets of the instant claims are those wherein the tablet has very low concentration of active principle, and very little in the way of excipients, coatings, and the like. The functional components of the tablets include only coated neutral microgranules, a lubricant, and, in one embodiment, a film coating on the fully fabricated tablet. The only coating on the neutral microgranule is a solitary and substantially homogeneous coating of the active principle, optionally mixed with a binder. The coated neutral microgranules are directly compressible, and form substantially the entirety of the content of the tablet, e.g., 99-100% (wt). The only other permissible component of any substance or function in the tablet is a small quantity of lubricant, i.e., 1% or less by weight of the entire tablet. The instant claims are thus directed to tablets or tablet premixes that exclude any substantial functional component other than the coated neutral microgranules and 1% or less lubricant; and the coated neutral microgranules exclude any substantial functional component other than the active principle and an optional binder, thereby excluding components such as protective polymers, dispersants, and the like.

The tableting and premix claims as now presented do not introduce new matter. Among other things, the claims are now structured to eliminate components in the tablet or the tableting premix beyond the neutral microgranules, the coating of active principle and optional binder, and less than 1% lubricant. As such, the claims exclude neutral microgranules coated with agents modifying the release and/or masking the taste of the active principle. *See, e.g.,* Specification, p. 10, lines 22-30 (explaining that "the active principle is attached as a coating to the neutral

microgranules and is not coated with an agent intended to modify its release or to mask its taste.").

The cited prior art does not meet those limitations. Each of the cited references teaches that additional components are necessary to the fabrication of suitable tablets.

Bhutani

Bhutani states:

> Thus, according to the present invention, the active ingredient is first coated onto non-pareil beads or onto drug crystals or granules. These pellets are then divided into several groups *and varying amounts of retarding materials are applied to different groups*. Upon subsequent mixing of the groups, the combined effect of the total pellets will provide gradual release of the medicine. These pellets are then cured in the oven to stabilize the release rates.
>
> The stabilized pellets are then coated with several layers of disintegrating agent or agents and compressed into tablets or pills, after adding a small amount of lubricants or other inert ingredients, if necessary.

Col. 4, lines 11-24.

Bhutani thus teaches that the mixture of coated pellets are not compressible into tablets until they have been "coated with several layers of disintegrating agent or agents", after which one might add a lubricant or other inert ingredient. Despite the teaching of Example 4, *Bhutani* does not teach that the coated neutral microgranules themselves are directly compressible as required by the instant claims. Quite the contrary, the reference teaches that the neutral microgranules must first be cured in an oven to stabilize the pellets, and the stabilized pellets must then be subject to additional coating with *several layers* of disintegrating agent or agents. Thus, the coated pellets of *Bhutani* do not meet the requirements of the instantly claimed

premixes as they are not taught to be directly compressible when coated only with active principle; and when they are compressible, they have multiple layers of various ingredients, notably disintegrating agents. Accordingly, *Bhutani* does not teach or suggest the claimed premixes.

In like fashion, the claimed tablets (claims 19-27 & 33) are not anticipated by *Bhutani* in that the tablet of *Bhutani* is necessarily composed of coated neutral microgranules wherein the coating on the neutral microgranules includes the various disintegrating agents coating solutions, or the like. Accordingly, *Bhutani* does not teach the subject of the tablet claims, and particularly that of claim 33, which expressly excludes any agent modifying release of the active principle or masking its taste.

Harrison

Harrison also fails to teach or suggest the claimed invention, whether in the form of the premix claims or those of the tablet, per se. *Harrison* requires the presence of other additives and layers of materials that are excluded by the instant claims.

Harrison Requires the Presence of Release-Rate Controlling Additives

Premix claim 32 and tablet claim 33 both require that the subject matter excludes coatings or agents modifying release of the active principle or masking its taste. *Harrison* expressly requires the presence of such agents. *Harrison* teaches that the medicament-coated inert particulate cores must have a further "sustaining coating", which must contain three polymers, each of which behaves differently in the gastrointestinal tract: the first being soluble at all pH values normally

encountered in the gastrointestinal tract; the second being insoluble at pH values below about 5.0, but soluble above that value; and the third being insoluble at all pH values normally encountered in the gastrointestinal tract. *E.g.*, col. 5, lines 12-59.

Harrison expressly teaches that a number of discrete polymers must be added, and that those three polymers must be carefully selected for their solubility at various pH values as found in various portions of the gastrointestinal tract. Those agents are expressly taught to be selected for their ability to affect the rate of release of the medicament. *See, e.g.,* col. 5, lines 12-59; *see also* lines 60-65 ("The polymer ratios have an *important bearing* upon the rate of release of medicament at all pH values. Increase in the ratio of the first polymer to the third polymer raises the rate of release of medicament at all pH values, whilst decrease in this ratio reduces the rate of release." (emphasis added)). Thus, *Harrison's* requisite inclusion of at least three polymers violates the requirement of the instant claims that the coated neutral microgranules must not include an agent modifying release of the active principle or masking its taste.

Harrison's Release Rate-Controlling Agents Are Excluded by Claims 19-27

Nor does *Harrison* teach the subject matter of tablet claims 19-27. The subject of instant tablet claims 19-27 require that the tablet includes only coated neutral microgranules and optional lubricant (≤1% wt); that the coated neutral microgranules are directly compressible; that the coated neutral microgranules have only a single layer coating; and that the single layer includes only active principle and optional binder. Substantial quantities of other functional components are excluded by the transition phrase "consisting essentially of."

Harrison teaches that such other components (*i.e.*, the three release rate-controlling polymers) are crucial, and that they have an "important bearing upon the rate of release of medicament." As shown above, the inclusion of three or more polymers selected to affect the release rate of the active principle, as taught by *Harrison*, is excluded from the instant claims. Accordingly, *Harrison* fails to teach the subject of the tablet claims 19-27.

Harrison's resulting tablets also necessarily include particulate cores having more than a single layer coating. *Harrison's* medicament-coated particulate cores necessarily include an additional "sustaining coating" of separate and distinct additives (polymers), which collectively have an "important bearing" on the operation and function of the resulting tablet. *E.g.*, Col. 3, lines 53-56 ("... each bead of said medicament-coated inert particulate core is surrounded by a sustaining coating comprising at least three admixed polymers...."). Such multi-layered tablets are expressly excluded by the plain language of claims 19-27, which limits the structure of the neutral microgranules to those having a single layer of a coating containing only active agent and optional binder. Thus, *Harrison* fails to teach the subject of the instantly claimed tablets.

Harrison Does Not Teach the Tableting Premix Claims

Harrison also fails to teach the tableting premix of instant claims 28-29 (and, as shown above, 32). To the extent that *Harrison* teaches something analogous to a tableting premix, the reference teaches that the coated neutral microgranules that are compressible into the resulting tablet must also include the sustaining coating of

at least the three polymers that "have an important bearing upon the rate of release of medicament."

Harrison does not teach that the particulate cores suspended in the Pharmacoat 606 mixture is a directly compressible formulation when compounded with only active principle. Instead, *Harrison* teaches that it is essential that the coated neutral microgranules have a further "sustaining coating", and that coating must contain at least three distinct polymers. *E.g.,* col. 5, lines 12-14 ("The sustaining coating essentially contains three polymers each of which behaves differently in the gastrointestinal tract."); and col. 4, lines 53-56 ("Consequently the particular polymers used and their proportions in the sustaining layer will determine the release characteristics of the medicaments from the dosage form."); *see also* col. 6, lines 29-64 (explaining that coated neutral microgranules of "Preparation A" were subsequently coated with an ethanolic solution of ethylcellulose, hydroxypropylmethylcellulose and hydroxypropylmethylcellulose phthalate). Thus, the tablet mixture of *Harrison*, insofar as it is taught to be compressible into functional tablets, necessarily includes neutral microgranules coated with at least two discrete layers, at least one of which contains numerous additional ingredients. Both the structure of the added layer and the additional ingredients are expressly excluded by the language of the instant claims.

Harrison does not teach or suggest a directly compressible tableting premix consisting essentially of coated neutral microgranules containing only a singular coating of the active agent and binder (*e.g.*, Pharmacoat 606). Thus, *Harrison* fails to teach the claimed tableting premix.

Frost and *Makino*

Frost and *Makino* fail to suggest the claimed tablets of new tablet claims 19-27, or 33. Those claims expressly require that the claimed tablets are coated neutral microgranules, wherein the coating is restricted to a single layer, and the single layer is restricted to the active principle and an optional binder, and wherein the tablet itself might further include up to 1% by weight lubricant.

Frost teaches a pharmaceutical composition having a "plurality of dosage subunits (e.g., coated nonpareil seeds) each having at least two components including a component of [active principle] and an outer pharmaceutically inert component stable in acidic pH which dissolves in a basic pH, whereby upon oral administration of said pharmaceutical composition the [active principle] is not exposed to gastrointestinal fluids until the small intestine." *Frost*, p.1.

Frost teaches the use of a methylmethacrylate coating over the active principle to protect the active principle, and to prevent its dissolution at least until reaching the small intestine. (*e.g.,* Examples III & IV).

Similarly, the subject of Example VII of *Frost* fails to teach or suggest the claimed invention. In Example VII, *Frost* describes compressing together the dosage subunits of Example II and hydroxypropylmethylcellulose (HPMC). The dosage units of Example II are those wherein nonpareil seeds were wetted with alcohol-dissolved Kollidone 90 (BASF), and then repeatedly dusted with 2', 3' - didesoxyadenosine. Those coated granules are then combined with HPMC in a ratio of 10:1.

This likewise teaches away from the claimed invention. First, the resulting tablet of Example VII does not comprise a tablet consisting essentially of coated

neutral microgranules and an excipient, wherein the coating of the neutral microgranule consists essentially of a single layer of an active principle mixed with optional binder. In *Frost*, there is first an adhesive layer of Kollidone dissolved in alcohol on which is dusted an active principle, thus forming two separate and discrete layers, which is proscribed by the instant claims.

Further, there is in *Frost* the added component of the HPMC added in substantial quantities and separate from the single layer of active principle and optional binder on the nonpareil seeds. The HPMC of *Frost* is proscribed by instant claims 19-27 in that it is not a part of the single layer coating on the neutral microgranules; and further it is added in a ratio of 10% by weight of the composition. As such it cannot be said to merely fill the role of the unspecified binder, as it is not within the single layer coating of the neutral microgranules; and it cannot be said to fill the role of the lubricant as it is present in quantities far exceeding that specified by the instant claims. Thus, the HPMC of *Frost* Example VII is a substantial quantity of an added component outside the single layer of the active principle and optional binder, and it is added for a functional and substantive purpose. *Frost* thus clearly teaches away from the claimed invention by showing that the described coated non-pareil seeds, themselves, are unsuitable for manufacturing a pharmaceutical composition without added protective and release-modifying layers, or without substantial additional components mixed into the tablet to otherwise minimize exposure of the active principle to gastrointestinal fluids.

Frost teaches that the composition must include a component that controls release of the active principle, in violation of the requirements of claim 33; and further includes a component in the form of a layer having something other than the

active principle and a binder on a neutral microgranule, in violation of the requirements of claim 19, and its dependent claims 20-27.

Makino does not cure the deficiencies of *Frost*. *Makino* has not been shown to teach or suggest that the nonpareil seeds of *Frost* can dispense with the added layer *Frost* includes to prevent exposure of the active principle to gastrointestinal fluids; nor has it been shown to teach or suggest that one can dispense with the substantial quantities of HPMC mixed into the tablet with the coated seeds to otherwise protect and minimize exposure of the active principle on the surface of the seeds to gastrointestinal fluids.

It has been argued that the HPMC of *Frost* could be considered the formerly recited "excipient"; and it would have been a matter of routine optimization to reduce the HPMC of *Frost* to 1% or less as claimed. The instant claims, however, now recite that the excipient is a lubricant, and there has been no showing that HPMC could fulfill such a role. Further, even under the former claim construct, there has been no showing of any teaching in the art that would have led one skilled in the art to reduce the quantity of HPMC recited in *Frost* to levels specified in the claims (*i.e.*, $\leq$1% wt).

Makino does not provide that teaching. Indeed, *Makino* teaches squarely away from such a development. *Makino* teaches that the cellulosic additive used therein (L-HPC) should be included in the range 5-90%, and preferably 10-60%. Thus, *Makino* teaches away from the claimed invention, consistent with *Frost*, in suggesting that far greater quantities of L-HPC be used.

Further, *Makino* teaches away from the current claimed tablets, and contrary to that asserted in the outstanding rejection. The L-HPC of *Makino* is included in the

formulation as commingled with the active agent, and that spraying powder is added to seed cores that have already been coated with an aqueous binder; thus, that embodiment has an additional binder layer that is proscribed by the instant claims.

It has also been argued that the cellulosic additive of *Makino* could fulfill the claimed element of the lubricant, and that it would have been obvious to reduce that constituent to 1%. As described above, the latter part of the argument fails as *Makino* teaches away from the asserted "optimization", and in fact urges substantially greater quantities, *e.g.*, 10-60%.

Equally importantly, *Makino* teaches away from the assertion because, according to *Makino* that cellulosic material (L-HPC) is included in the coating layer (along with other binders, adhesives, and the like; see, e.g., col. 3, lines 36-44), and thus cannot fulfill the role of both binder and lubricant as the lubricant is necessarily separate and distinct from the single layer of active principle and optional binder. As such, *Makino* cannot be said to teach or suggest those elements missing from *Frost,* and the obviousness rejection fails. Applicants request reconsideration and withdrawal of the obviousness rejection, particularly in light of the newly presented claims.

Conclusion

In view of the foregoing amendments and remarks, Applicant submits that the application is in condition for allowance. By this Request for Continued Examination and Submission, Applicant withdraws the pending Appeal. Applicant requests substantive examination of the claims presented herein, reconsideration and withdrawal of all outstanding rejections, and formal notification of allowance. If the

Examiner perceives any impediment to such formal notification of allowance, whether formal or substantive, Applicant asks the Examiner to telephone Applicant's representative at the number provided below. Such informal communication will expedite examination and disposal of the case.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

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